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09/137,059	08/20/1998	BRIAN JOHNSTON	A-65200/WHD/	2454

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EXAMINER
SCHMIDT, MARY M

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/137,059	Johnston et al.
Examiner	**Art Unit**
Mary Schmidt	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jul 29, 2002* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *23-49* is/are pending in the application.

4a) Of the above, claim(s) *27, 29-31, 33, and 37* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *23-26, 28, 32, 34-36, and 38-49* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's election without traverse of the following species present in claims 23-26, 28, 32, 34-36 and 38-49: (I) **DNA (including ssDNA)** (instead of RNA, polypeptides, aptamers or metal ions) as the target molecule; (II) **hairpin** (instead of hammerhead) as the type of catalytic RNA; and (III) **not bound to the catalytic RNA** (instead of bound to the catalytic RNA or autocatalytic) as the location of the substrate in Paper No. 32, filed 12/06/01, is acknowledged.

Claims 27, 29-31, 33 and 37 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 32, filed 12/06/01. Specifically, claims 27, 29, 30 and 31 are drawn to species not elected in section (I); claim 33 is drawn to a species not elected in section (II); and claim 37 is drawn to a species not elected in section (III).

2. This application contains claims 27, 29-31, 33 and 37 drawn to an invention nonelected with traverse in Paper No. 32, filed 12/06/01. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 23-26, 28, 32, 34-36 and 38-49 are pending for consideration on the merits.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 23-26, 28, 32, 34-36 and 38-49 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the same reasons of record as set forth in the Official Action mailed 02/14/01, and 02/27/02.

Applicant's arguments filed 07/29/02 have been fully considered but they are not persuasive.

Claims 23, 32, 34-36, 38, 40, 45 and 48 have been amended to state that the RNA molecule comprises a catalytic domain and that the catalytic action is a catalytic domain of a hairpin ribozyme and/or the catalytic action comprises both cleavage and ligation of nonadjacent substrates; wherein the catalytic action comprises cleavage of a capture probe which is bound to the target and ligation of two replicase probes which are not bound to the target; wherein the catalytic action comprises cleavage of the substrate and wherein a portion of the capture probe is released from the solid support upon said cleavage; wherein said catalytic action comprises ligation of the two replication probes to each other.

In previous Official Actions, it has been argued that the specification as filed teaches Antisense-triplex-Ribozyme (ATR) molecules which have improved binding capacity over an

Antisense-Triplex (AT) to the same "target". However, it is not clear how these types of constructs function to "act" on any other substrate (than the "target") as instantly claimed. As pointed out previously, on page 4 of the specification, it is taught that the "sense-antisense hybridization is unstable in the absence of the clasp molecule... the ends of the padlock DNA create a binding site for c-myc." And on page 3 it is taught that "the ball represents any of various ways for the ends of this molecule to interact following hybridization with the target with creation of at least one turn of helical interwinding.... In one embodiment, the ball comprises a hairpin ribozyme moiety." In the specific case of the ATR example, it is not clear that the ATR (specifically the R, the ribozyme) acts on a substrate other than the target which the ATR complex binds. And since the claim specifies a transition from a catalytically inactive to a catalytically active RNA, it is not clear what substrate the RNA is cleaving. The example of the c-myc binding does not qualify as a transition from a catalytically inactive to active RNA.

Applicants traverse the rejection by pointing to regions of the specification which teach prophetically the design of the RNA molecule, target and substrate compositions instantly claimed. However, Applicant does not address how the claimed RNA molecule goes from catalytically in active to catalytically active, how the binding to c-myc is representative of binding to a substrate other than target, and further, how the various probe compositions act to bind a target (such as c-myc?) or not bind a target such that the catalytic RNA molecule may still become catalytically active. Furthermore, in view of the claim amendments, it is unclear what

probes that RNA molecule is ligating such that the ligated probes may serve as a substrate for Qbeta replicase as newly claimed.

In the instant response filed 7/29/02, Applicant states that "the Office Action fails to address Applicant's previous argument that the claimed invention is enabled by the disclosure in Example VI of the specification. Applicants respectfully reiterate that guidance regarding how to make and use the claimed invention is provided in Example VI of the specification (p. 56, line 29-p. 71, line 24) and in Figures 25-29, 21, 32. Example VI describes target-dependent RNA catalysis as a means for detection and amplification of target molecules."

Example 6 is a example encompassing prophetically many different methods such as PCR, Qbeta-replicase cycling; "design and construct[ion], using randomization and selection procedures, a latent hairpin ribozyme derivative becoming catalytically active only after binding to a target sequence (Figure 29)...[t]he ultimate goal is to design a scheme for nucleic-acid based diagnostics that can be used to detect either DNA or RNA, is sensitive, rapid, requires no thermal cycling, and readily lends itself to automation (page 57).... In this approach (page 61), we combine the best features of these two approaches by employing a hairpin ribozyme construct for the target-dependent-ligation of two halves of a split substrate for Qbeta-replication.... because the hairpin ribozyme can catalyze both ligation and cleavage (see below), it can play dual roles of target-dependent ligase and specific endonuclease." On page 62 applicant teaches by way of example two HPR constructs, HPR1 and HPR2 which "cleave and ligate adjacent or distant substrate sequences on the same RNA strand (reaction in cis), as well as to ligate substrates on

separate molecules (reaction in trans)...." However, applicant teaches that these two effects were demonstrated in different reactions, a separate cleavage reaction from a ligation reaction (presumably having different buffers, etc. to assist the hairpin molecule in a certain reaction). These examples further do not provide a clear picture of the entire method claimed by applicant. The disclosed examples are instead primarily prophetic in nature. For instant the "synthesis of RNAs with appropriate ends" section on pages 65 and 66 states that the "replication probes must have 5'-OH and 2',3'-cyclic phosphate ends in order to be ligated by HPR domain E. Applicant further states that "[t]he above described scheme will be tested using as target a sequence from the pol gene of HIV-1.... We must also design a derivative of HPR that has catalytic activity dependent on target binding.... (Page 66) To make catalytic activity dependent on target binding, we substitute a Y-branch for the closed loop and select a sequence that will not support catalytic activity unless the target is accurately paired. The scheme for selecting sequence NNNN is an in vitro selection and amplification procedure... based on sequential RNA-catalyzed cleavage and ligation reactions.... (continuing on page 67) Having obtained good candidates for the target-dependent catalytic moiety, the next step will be to demonstrate its ability to cleave a separate RNA (in trans) if the two RNAs are hybridized to adjacent sequences on a target RNA. For this purpose we will construct DNA templates for the transcription of target RNA spanning the region of HIV to which all the probes bind.... etc.

In essence, while Applicant has shown creation of certain hairpin molecules, applicant has not reduced to practice the bulk of the asserted method steps for design and use of such hairpin ribozymes to have catalytic action on a substrate other than the target molecule in trans.

To make and use the claims as amended which specify wherein the catalytically inactive RNA molecule allows catalytic action upon a substrate (not bound to the catalytic molecule) other than the target, one skilled in the art would necessarily practice further basic research to follow the experiments in Example 6. For instance, the disclosure that one skilled in the art would need to use *in vitro* evolution to identify significant regions of the hairpin molecules for use in the claimed methods necessitates the practice of basic research to identify novel and undisclosed sequences and mechanisms of use of such sequences.

As such, in view of the lack of guidance in the specification as filed to make and use specific compositions which act as catalytic molecules on substrates other than a target molecule, in trans, one skilled in the art would necessarily practice "trial and error" experimentation to make such molecules. Although the art teaches probes which bind target nucleic acids, the art does not provide guidance on how to modify the teachings of the instant specification such that hairpin ribozymes may be used to ligate such probes for detection of another target molecule as instantly claimed absent further research suggested in the disclosure of the instant invention. Without substantive guidance in either the specification or the art to make and use the claimed molecules together as claimed, one skilled in the art would necessarily practice undue experimentation to make and use the claimed invention.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

6. Claims 23-26 and 28 stand rejected under 35 U.S.C. 102(e) as being anticipated by Bekkaoui et al. (U.S. Patent 6,136,533)for the same reasons of record as set forth in the Official Action mailed 02/27/02.

Applicant's arguments filed 07/29/02 have been fully considered but they are not persuasive.

Claim 23 has been amended to state that the RNA molecule comprises a catalytic domain and that the catalytic action is a catalytic domain of a hairpin ribozyme and/or the catalytic action comprises both cleavage and ligation of nonadjacent substrates.

Bekkaoui et al. teach a method for detecting the presence of a target molecule in a composition suspected of containing said target molecule (abstract), said method comprising: contacting said composition (the target nucleic acid and single stranded nucleic acid probe (abstract) with an enzyme capable of cleaving the probe (ie. encompasses a catalytically inactive

RNA molecule), wherein binding of said enzyme (ie. catalytically inactive RNA molecule) to said target molecule allows said enzyme to become catalytically active, and cleave a double-stranded target-probe complex at a scissile linkage (the substrate other than the target molecule, and bound to the target), wherein the action of the enzyme on the substrate is indicative of the presence of the target in said composition (see abstract and also col. 4, lines 52-66 for types of target nucleic acids).

Applicants state on page 9 of the response that "[a]ll of the working examples provided int he specification involve use of RNase. There is no disclosure of any "enzyme" other than RNASE H and no disclosure or suggestion of use of a catalytic RNA molecule for catalysis. In contrast, in the presently claimed invention, catalysis is performed by an RNA molecule with a catalytic core. Further... RNase H does not possess latent catalytic activity that is depend[ent]] upon binding to a target. In contrast, the present claims recite a catalytically inactive RNA molecule which must bind to the target for catalytic action upon the substrate to occur."

In response, applicant is reminded on MPEP 2111.01 which states that "[w]hile the meaning of claims of issued patents are interpreted in light of the specification, prosecution history, prior art and other claims, this is not the mode of claim interpretation to be applied during examination. During examination, the claims must be interpreted as broadly as their terms reasonably allow." In the instant case, the claims do not specify what type of "catalytic domain" the RNA molecules have. It is within reasonable interpretation of the claim language, that a non-ribozyme catalytic event of the broad claims is embraced by the claims which merely

state that "said RNA molecule comprises a catalytic domain, wherein binding of said catalytically inactive RNA molecule to said target molecule allows catalytic action upon a substrate other than the target molecule." Furthermore, the disclosure of '533 does embrace hairpin structures in the disclosed probes in col. 12, lines 56-65 for instance.

7. Claims 23-26, 32, 38-40 stand rejected under 35 U.S.C. 102(b) as being anticipated by Stefano et al. (U.S. Patent 5,472,840) for the same reasons of record as set forth in the Official Action mailed 02/27/02.

Applicant's arguments filed 07/29/02 have been fully considered but they are not persuasive.

Claims 23, 32, 38 and 40 have been amended to state that the RNA molecule comprises a catalytic domain and that the catalytic action is a catalytic domain of a hairpin ribozyme; wherein the substrate comprises a capture probe which comprises polynucleotide sequences that are complementary to both the target sequence and the substrate sequence; wherein the catalytic action comprises cleavage of the substrate and wherein a portion of the capture probe is released from the solid support upon said cleavage; wherein said catalytic action comprises ligation of the two replication probes to each other.

Stefano et al. teach a method for detecting the presence of a target molecule in a composition suspected of containing said target molecule (see col. 4, lines 17-61 for how to detect a DNA target), said method comprising: contacting said composition with a catalytically inactive RNA molecule which binds to said target molecule, wherein binding of said catalytically

inactive RNA molecule to said target molecule allows said catalytically RNA molecule to become catalytically active toward a substrate other than the target molecule (see col 17 though col. 19 for a description of the types of target, probe and ribozyme reactions taught), wherein the action of the catalytically active RNA molecule on the substrate is indicative of the presence of said target molecule in said composition. (See also example 4, cols. 23-24 and col. 26, lines 28-30 for description of a capture probe captured on a solid support).

Applicant again traverses the art rejection on the grounds that the reference does not "disclose each and every element of a claimed invention." Specifically, applicant states that "stefano does not anticipate because the disclosed methods do not include the claimed elements of binding of a catalytically inactive RNA molecule comprising a catalytic domain to a target, or do not include catalysis dependent upon binding of the RNA molecule to the target."

In response, the rejection is again maintained in view of MPEP 2111.01 as cited above. Stefano does not need to teach the exact mechanism of action disclosed in the specification as filed. Stefano does teach use of ribozymes in col. 8, lines 51-67, where "probes bearing the ribozyme may be efficiently produced..." Although the mechanism of action of the ribozymes taught therein is a coming together and a separation "allowing the first section to become active...." (Col. 9, lines 1-5) such mechanism of action is embraced by the breath of the instantly claimed methods in view of the open "comprising" language. In col. 11, lines 10-20, they further teach hairpin ribozymes which "allows such sections and areas to form "stem" loops which open up only on interacting with target, rendering such first and second nucleic acids incapable of

forming a ribozyme without specific target interaction." Such methods continue to read on the instant claims as amended since the catalytically inactive RNA molecule binds to target in the instant claims as well (but does not bind to substrate), and it is within the reasonable interpretation of the claim language to visualize wherein the catalytically inactive RNA molecule, once bound to target is thus allosterically transformed into an active molecule just as taught in the '840 reference.

Applicant further states that "catalysis by the ribozyme... is promoted by imposition of external "ribozyme reaction conditions." In contrast, the present claims recite that the binding of an RNA molecule to a target allows catalytic action upon the substrate. No other change of "ribozyme reaction conditions" is required." However, as pointed out above, the '840 reference does provide a simple example of the allosteric change in ribozyme activity. Furthermore, the claims as broadly written, with comprising language, embrace additional method steps not explicitly recited in the instant claims.

8. Claims 34-36 and 41-49 are free of the prior art since the art does not teach nor fairly suggest modification of the Bekkaoui et al. or Stefano et al. references for ligation of probes by the claimed methods nor amplification of such substrates after ligation by Q beta replicase in the context of the instantly claimed methods.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Receptionist, whose telephone number is (703) 308-0196.

M. M. Schmidt
October 21, 2002

JOHN L. LeGUYADER
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